UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/560,357	12/12/2005	Hiroshi Tomiyama	TAN-356	8894

7590 10/08/2008

H. Jay Spiegel and Associates PC
P.O. Box 11
Mount Vernon, VA 22121

EXAMINER
BLAND, LAYLA D

ART UNIT	PAPER NUMBER
1623	

MAIL DATE	DELIVERY MODE
10/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,357	TOMIYAMA ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2008*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6,9,11,13,15,16,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-6, 9, 11, 13, 15, 16, 18, 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is a response to Applicant's amendment submitted July 2, 2008, wherein claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18, and 19 are amended and claims 3, 7, 8, 10, 12, 14, 17, and 20-28 are canceled. Claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18, and 19 are currently pending and are examined on the merits herein.

Applicant's submission of the English translation of Japanese priority document 2003-185171 is acknowledged.

In view of the cancellation of claims 2, 4-6, 9, 11, 13, 15, 16, 18, and 19, all rejections made with respect to those claims in the previous office action are withdrawn.

In view of Applicant's remarks submitted July 2, 2008, the objection to claim 2 as being a substantial duplicate of claim 1 is withdrawn.

In view of Applicant's amendment submitted July 2, 2008, the rejection of claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18, and 19 under 35 USC 112, second paragraph is withdrawn.

The following rejection is maintained:

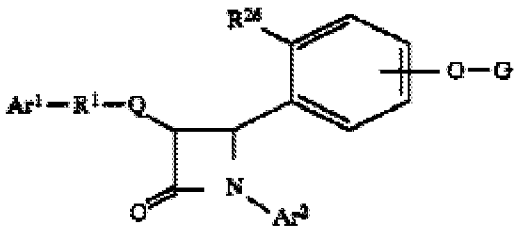
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-6, 9, 11, 13, 15, 16, 18, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yumibe et al. (US 5,756,470, May 26, 1998) and Tomiyama et al. (US 2004/0063929, April 1, 2004, PTO-1449 submitted April 25, 2006, English equivalent of WO02/066464, published August 29, 2002).

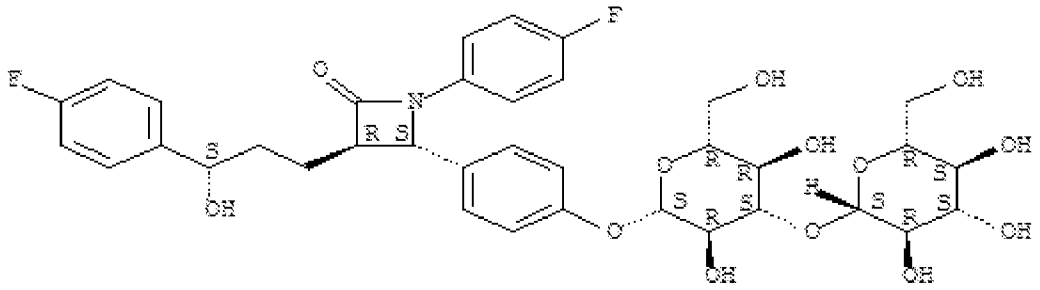
Yumibe et al. teaches a combination of a cholesterol biosynthesis inhibitor and a β-lactam cholesterol absorption inhibitor for lowering cholesterol and treating or preventing atherosclerosis [see abstract]. The combination of a beta-lactam cholesterol absorption inhibitor and HMG CoA reductase inhibitor results in a greater decrease in plasma cholesterol than either agent alone [column 2, lines 11-20]. Suitable cholesterol biosynthesis inhibitors include HMG CoA reductase inhibitors, squalene synthesis inhibitors, and squalene epoxidase inhibitors [column 2, lines 51-63 and claim 20]. The genus of compounds taught by Yumibe et al. is as follows [column 2]:



Wherein R^{26} is H or O-sugar, G is a sugar, and Ar^1 and Ar^2 are aryl or substituted aryl. Specific embodiments are claimed in claim 13 and include, among others, the following:

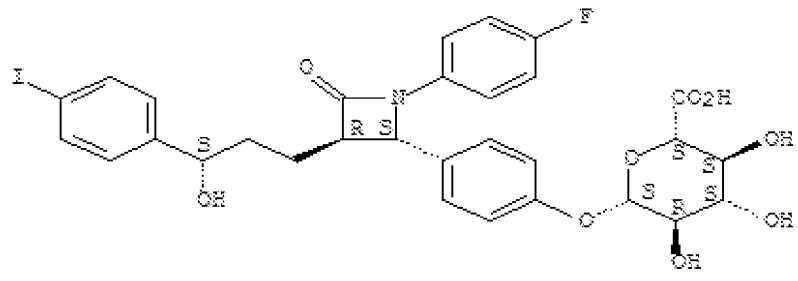
L2 ANSWER 3 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 208259-77-2 REGISTRY
ED Entered STN: 09 Jul 1998
CN 2-Azetidinone, 1-(4-fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-[4-[(3-O-β-D-glucopyranosyl-β-D-glucopyranosyl)oxy]phenyl]-, (3R,4S)- (CA INDEX NAME)
FS STEREOSEARCH
MF C36 H41 F2 N O13
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



L2 ANSWER 11 OF 45 REGISTRY COPYRIGHT 2008 ACS on STN
RN 180448-79-4 REGISTRY
ED Entered STN: 27 Jun 1997
CN β-D-Glucopyranosiduronic acid, 4-[(2S,3R)-1-(4-fluorophenyl)-3-[(3S)-3-hydroxy-3-(4-iodophenyl)propyl]-4-oxo-2-azetidinyl]phenyl (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H29 F I N O9
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

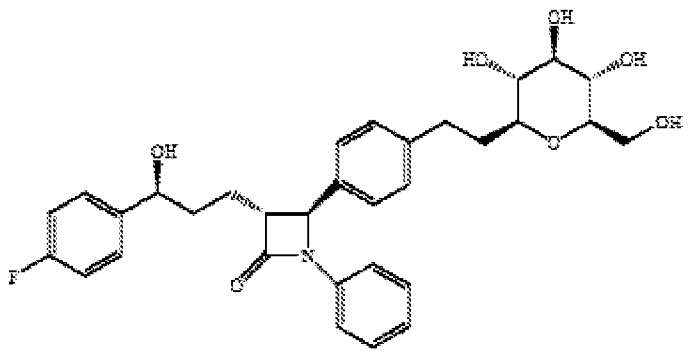


Pharmaceutical compositions comprising the compounds of Yumibe et al. and a cholesterol biosynthesis inhibitor are specifically claimed [claims 15 and 16].

The difference in the beta-lactams taught by Yumibe et al. and the instantly claimed beta-lactams is that the instantly claimed lactams comprise C-glycosides and those of Yumibe et al. comprise O-glycosides.

Tomiyama et al. teach beta-lactam compounds which are useful as serum cholesterol-lowering agents and which meet the limitations of the instant claims [see abstract and columns 2-3, and structures in columns 7-36]. Tomiyama et al. teach that O-glycoside bonds in beta-lactam-O-glucuronate compounds can be hydrolyzed in the small intestine, possibly reducing the activity of the compounds [column 1, lines 51-62]. Beta-lactams having a C-glycoside, which is stable to metabolism by glycosidase and hydrolysis, were prepared [column 2, lines 3-10]. One preferred compound, compound 56 [column 35], shown below, is the same compound as that which is recited in instant claim 4:

56



Other preferred compounds include compound 37 [column 25], which is the same compound as that which is recited in instant claim 5.

Tomiyama et al. do not teach a combination of beta-lactam and cholesterol biosynthesis inhibitor.

It would have been obvious to one of ordinary skill in the art to prepare a cholesterol-lowering composition comprised of a cholesterol biosynthesis inhibitor and a β-lactam taught by Tomiyama et al. The combination of beta-lactam cholesterol absorption inhibitor and cholesterol biosynthesis inhibitor is already known in the art, as taught by Yumibe et al. Tomiyama et al. teach modified beta-lactams which are ideal cholesterol absorption inhibitors with low incidence of side effects [column 1, line 65 - column 2, line 2]. One of ordinary skill in the art could have substituted Tomiyama's modified beta-lactams for the beta-lactams in the combination taught by Yumibe et al. and would have predicted that the resulting composition would be effective for reducing plasma cholesterol levels and treating atherosclerosis.

Further, both cholesterol biosynthesis inhibitors and the β-lactams taught by Tomiyama et al. are known in the art for reducing serum cholesterol levels. It is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose. In re Kerkhoven, 626 F.2d 846, 205 U.S.P.Q. 1069 (C.C.P.A. 1980).

Response to Arguments

Applicant presents Exhibits A and B and argues regarding the pharmacology of Yumibe's compounds in light of those exhibits. Yumibe teaches O-glycosides. Exhibits A and B are drawn to the activity of ezetimibe (Zetia or SCH58235), which is not a glycoside and is not one of Yumibe's compounds. The activation in the intestine, mentioned in Exhibit A, relates to SCH58235, ezetimibe, as does the discussion of side effects mentioned in Exhibit B. Applicant's arguments regarding ezetimibe are not relevant to the rejection.

Applicant argues that there is nothing to suggest a combination of the C-glycoside beta lactams of Tomiyama et al. with cholesterol biosynthesis inhibitors because the O-glycoside beta-lactams of Yumibe et al. are known to exhibit undesirable side effects in combination with cholesterol biosynthesis inhibitors. Applicant's argument is not persuasive because Tomiyama et al. teach that the C-glycoside beta lactams have a low incidence of side effects. Furthermore, Exhibit B, which Applicant relies upon for the teaching of side effects, is not drawn to the compounds of Yumibe.

Applicant argues that Tomiyama teach away from Yumibe because O-glycoside beta-lactams as disclosed by Tomiyama are known to exhibit undesirable side effects in combination with cholesterol biosynthesis inhibitors. It is noted that Tomiyama teaches C-glycosides. Tomiyama's C-glycosides are taught to have a low incidence of side effects. Furthermore, Exhibit B, which Applicant relies upon for the teaching of side effects, is not drawn to the compounds of Yumibe or Tomiyama.

Applicant argues that the claimed combination of C-glycoside and cholesterol biosynthesis inhibitor is synergistic. Yumibe teaches that the combination of a beta-

lactam cholesterol absorption inhibitor and HMG CoA reductase inhibitor results in a greater decrease in plasma cholesterol than either agent alone, so the skilled artisan would expect greater than additive effect.

Applicant argues that the action of C-glycosides of Tomiyama is different from that of ezetimibe and thus the synergistic effect would not be readily apparent. Applicant presents the table on page 24 of the response submitted July 2, 2008 to show a difference in HMG-CoA reductase activity between ezetimibe and a C-glycoside compound 56 of Tomiyama. Compound 56 is administered at roughly three times the dosage of ezetimibe, to which it is being compared. Furthermore, ezetimibe is not a glycoside and is not a compound taught by Yumibe. For these reasons, the comparison is not relevant and Applicant's arguments are not persuasive.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Tuesday - Friday, 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner, Art Unit 1623

/Layla Bland/
Examiner, Art Unit 1623